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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,744	10/05/2001	Marcel P. Bruchez	5100-0702	4380

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EXAMINER

DO, PENSEE T

ART UNIT PAPER NUMBER

1641

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/972,744

Applicant(s)

BRUCHEZ ET AL.

Examiner

Pensee T. Do

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 11-14, 16-20, 25-35, 38 and 74-79 is/are pending in the application.
- 4a) Of the above claim(s) 16-20, 25-35 and 38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 11-14 and 74-79 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-6, 11-14, 16-20, 25-35, 38 and 74-79 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry & Claim Status

The amendment filed on April 5, 2006 has been acknowledged and entered.

Claims 1-6, 11-14, 16-20, 25-35, 38, 74-79 are pending.

Claims 16-20, 25-35, 38 are withdrawn from further consideration.

Claims 1-6, 11-14, 74-79 are being examined.

Information Disclosure Statement

The IDS filed on April 18, 2006 is not considered because there is no copy of the PTO/SB/08A form and there is no copy of the publication or reference cited attached.

Withdrawn Rejection(s)

Rejection under 102 by Bawendi is withdrawn herein.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 11-14, 74, 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Millard et al. (US 5,534,416) in view of Bawendi et al. (US 6,306,610).

Millard teaches a cell encoded with two different fluorescent dyes, dye 1 and dye 2. Dye 1 is highly membrane permeant and labels all cells. Dye 1 binds with intracellular nucleic acid polymers such as DNA and RNA and the resultant cell becomes extremely fluorescent upon illumination. (see col. 3, line 65-col. 4, line 18). Dye 2, which is detectably different than dye 1, stains the viable cells and such labeled cells give a fluorescent response inside the viable cells. (see col. 13, lines 60-65).

However, Millard fails to teach labeling the cell with a semiconductor nanocrystal; the detectable label comprises a semiconductor nanocrystal conjugated to a translocable molecule which is a ligand for a cellular receptor that enters the cell by endocytosis.

Bawendi teaches a composition comprising fluorescent semiconductor nanocrystals associated to a molecule such as cells, prokaryotic or eukaryotic. The semiconductor nanocrystals comprise a CdSe core and a ZnS shell. The composition is also associated with cell membranes. (see col. 3, line 60-col. 4, line 62; col. 19, lines 58-60; col. 20, lines 51-59; col. 29, lines 41-42). Bawendi also teaches nanocrystals coupled to antibodies to a cellular target/component. (col. 5, lines 10-17).

It would have been obvious to one of ordinary skills in the art to replace one of the fluorescent dyes in Millard with semiconductor nanocrystals of Bawendi because nanocrystals exhibit high fluorescent intensity (for detection in small quantities), a separation of at least 50 nm between the absorption and fluorescing frequencies, solubility in water, ability to be readily linked to other molecules, stability towards harsh conditions and high temperatures, symmetric, nearly Gaussian emission lineshape for

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easy deconvolution of multiple colors and compatibility with automated analysis.

Regarding claims 4-5, Millard (see col. 3, line 1) and Bawendi teach prokaryotic and eukaryotic cells (see col. 19, line 65), it would have been obvious to one of ordinary skills in the art to experiment cells such as yeast, mammalian cells of rat, mouse, bovine, hamster, and plant cell since it is well known that those cells are eukaryotic cells. Regarding claim 75, since Bawendi teaches that the nanocrystal can couple to a reagent for detection of biological compounds, organelles and studying endocytosis, it would have been obvious to one of ordinary skills in the art that such "reagent for detection of biological compounds, organelles" is a ligand for a cellular receptor that enters the cell by endocytosis because in order to study endocytosis, the cells must be labeled with the nanocrystal which in turn must be coupled to a ligand or a molecule that enters the cell membrane. It is well known that "endocytosis" is one of the methods for a compound to translocate across the cell membrane.

Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi et al. (US 6,306,610) as applied to claim 1, and further in view of Rothbard et al. (US 6,306,993).

Millard and Bawendi have been discussed above. In addition, Millard and Bawendi teach that the fluorescence dyes or semiconductor nanocrystals can associate with a molecule or reagent for detection of a biological compounds such as enzymes, DNA, RNA, cellular organelles, cell membrane molecules involved in signal transduction and such composition can be used to detect cell morphology and fluid flow,

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cell viability, proliferation and function; endocytosis and exocytosis. (see col. 20, lines 50-60).

However, Millard and Bawendi fail to teach the nanoparticle is conjugated to a ligand for a transporter.

Rothbard teaches methods and composition for transporting drugs and macromolecules across biological membranes wherein the biological membranes are contacted with a conjugate containing a biologically active agent (ligand) that is covalently attached to a transport polymer (transporter). Such transport polymer has 6 to 25 subunits of L-Arginine. The transport enhancing polymers are exemplified by peptides in which arginine residues constitute the subunits. Exemplary eukaryotic cell membranes of interest include membranes of dendritic cells, epithelial cells, endothelial cells, keratinocytes, muscle cells, fungal cells, bacterial cells, plant cells and the like. Biological active agents are macromolecules such as nucleic acids, peptides, proteins and analogs thereof. The agent may be linked to the polymer by a linking moiety. The composition includes a conjugate containing a biological active agent covalently attached to at least one transport polymer and can be packaged with instructions for using it. (see col. 2, line 44-col. 4, line 45; col. 5, lines 47-58). The transport polymers contain short-length polymers from 6 to 25 subunits. The conjugate is effective to enhance the transport rate of the conjugate across the biological membrane relative to the transport rate of the non-conjugate biological agent alone. (see col. 6, line 63-col. 7, line 5). Detecting uptake of macromolecules may be facilitated by attaching a fluorescent tag. (see col. 11, lines 3-4). Fluorescently labeled peptide polymers

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composed of 6 or more arginine residues entered cells more efficiently than the tat sequence 49-57 in fig. 1 (see col. 11, lines 30-40). Since the polymer of Rothbard composes of 6 to 25 contiguous Arg residues, it must be a cationic polymer.

Since Millard, Bawendi and Rothbard teach using a label such as nanocrystals and fluorescent dyes for cells or cell membrane, it would have been obvious to one of ordinary skills in the art to associate the polymer composition (comprising a ligand coupled to a transporter) taught by Rothbard to the nanocrystals as a fluorescent label and use in the combined composition taught by Millard and Bawendi because macromolecules such as peptides and oligonucleotides experience difficulty in passing across the biological membrane and having a polymer as a transportable molecule as that of Rothbard enhances trans-membrane transport. Furthermore, the nanocrystals of Bawendi can be used as a label that associates with the polymer to so that measures of biological molecules transported across the biological membrane can be easily detected because the nanocrystals of Bawendi associates with the biological membrane.

Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Rothbard as applied to claim 74 above, and further in view of Sodroski et al. (US 6,761,902).

Millard, Bawendi and Rothbard have been discussed above.

However, these references fail to teach that the translocatable molecule is a ligand for a G-protein coupled receptor (GPCR).

Sodroski teaches that G-protein coupled receptors (GPCR), which span the membrane seven times. These are functionally linked to signaling proteins known as G-proteins. (see col. 8, lines 13-52).

Therefore, it would have been obvious to one of ordinary skills in the art to couple the transmembrane receptor GPCR as taught by Sodroski to the "reagent for detecting biological compound" to study the endocytosis and exocytosis or to encode the cell as taught by Millard, Bawendi and Rothbard because the transmembrane receptor GPCR can cross the cell membrane seven times. Thus, study of endocytosis or exocytosis can be effectively performed.

Claim 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi et al. (US 6,306,610) as applied to claim 1, and further in view of Frankel et al. (US 5,652, 152).

Millard and Bawendi have been discussed above.

However, Millard and Bawendi fail to teach that the translocatable molecule is a HIV-Tat protein.

Frankel teaches intracellular delivery of cargo molecules by the use of transport polypeptides which comprise HIV tat protein or one or more portions thereof and which are covalently attached to the cargo molecules. The transport polypeptides are characterized by the presence of the tat basic region (amino acids 49-57). The biological active cargo molecules such as polypeptides, nucleic acids are delivered/transported into the cytoplasm and nuclei of cells in vitro and in vivo. (see abstract). Label such as a fluorescent was used to study the transported molecules

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across the cell membrane. The label is attached to the tat peptide. (see col. 42, lines 24-29).

It would have been obvious to one of ordinary skills in the art to use the HIV tat peptide for transporting biological molecules across the cell membrane as taught by Frankel and attach it to a fluorescence semiconductor nanocrystal which associates to a cell membrane or a subcellular organelle so that when biological molecules to be transported reach the cell membrane, they can be transported effectively and efficiently with the aid of the tat peptide and their activity or measurement can be detected by the nanocrystals since the nanocrystals have a spectral emission that is tunable to a desired wavelength, and wherein said wavelength provides information about a biological state or event.

Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Millard in view of Bawendi as applied to claim 1, and further in view of Barbera-Guillem (US 6,194,213).

Millard and Bawendi have been discussed above.

However, Millard and Bawendi fail to teach the composition further comprises a liposome.

Barbera-Guillem teaches a composition comprising functionalized nanocrystals and lipid membrane labeled such nanocrystals. Lipid membranes include cell membranes, liposomes, and lipid membrane-coated biosensors. (see col. 3, line 55-col. 4, line 20).

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It would have been obvious to one of ordinary skills in the art to use liposomes as a lipid membrane as taught by Barbera-Guillem in the combined composition of Millard and Bawendi since these references teach using nanocrystal and fluorescent dye to label lipid membrane or cell membrane. Liposome is well known as a carrier or delivery vehicle for drugs, proteins, or other compounds. Thus, having a liposome as part of the composition of Bawendi can transport the nanoparticles across the cell membrane.

Response to Arguments

Applicant's arguments with respect to claims 1-6, 11-14, 74-79 have been considered but are moot in view of the new ground(s) of rejection.

Although claim 15 was previously indicated allowable, after an updated search, relevant arts are found and applied to claim 15 which is the limitation that was incorporated in claim 1 in the previous response. The office apologizes for any inconvenience this may have caused.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
July 28, 2006


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